New era in recovery of bacterial pathogenicity

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Traditional treatment of infectious diseases is based on compounds that kill or inhibit growth of bacteria. A major concern with this approach is the frequent development of bacterial strains resistant to antibiotics. The discovery of communication systems (quorum sensing systems) regulating bacterial virulence afforded a novel opportunity to control infectious bacteria without interfering with growth. This study introduces not only a new mode of action and possible validation for traditional plant use, but also a potentially new therapeutic direction for the treatment of bacterial infections via inhibiting the bacterial virulence factors.

Keywords Anti-quorum sensing; multi-drug resistant; Gram negative bacteria

1. Introduction

Gram negative bacteria are responsible for many serious infectious diseases worldwide, including cystic fibrosis, pneumonia, obstructive pneumonia, bronchitis, microbial keratitis, chronic otitis infection, chronic corneal infections, urinary tract infection, chola, trachoma, plague, hemorrhagic E. coli disease, stomach ulcers, leonnaires disease, typhus, and dozens of others [1-5]. Although they cause different illnesses, Gram negative bacteria share certain disease inducing strategies.

2. Bacterial pathogenicity

Pathogenicity is the ability to produce disease in a host organism. Microbes express their pathogenicity by means of their virulence, a term which refers to the degree of pathogenicity of the microbe. Hence, the determinants of virulence of a pathogen are any of its genetic, biochemical or structural features that enable it to produce disease in a host [6, 7]. The relationship between a host and a pathogen is dynamic, since each modifies the activities and functions of the other. The outcome of such a relationship depends on the virulence of the pathogen and the relative degree of resistance or susceptibility of the host. Complex interactions between pathogen and host occur during the course of most infectious diseases. Microbes sense the host environment and produce virulence factors, such as toxins, that usually promote their growth and often lead to symptoms in the host [8]. Hosts sense the microbe and respond in various ways, such as activation of the innate immune response to eliminate the pathogen. The host molecules that microbes sense to trigger production of virulence factors are poorly understood [9, 10].

3. Pathogenicity islands

Pathogenicity islands may be located on the bacterial chromosome or may be a part of a plasmid. The finding that they are high in Guanine - Cytosine content, flanked by direct repeats i.e., the sequence of bases at two ends are the same. In addition they are associated with tRNA genes, which target sites for the integration of DNA, also they have characteristics of transposons in that they carry functional genes, e.g. integrase, transposase, or part of insertion sequences, and may move from one tRNA locus to another on the chromosome or plasmid., argue for the generation of pathogenicity islands by horizontal gene transfer (HGT), a process that is well known to contribute to microbial evolution [11].

Many bacterial virulence attributes, like toxins, adhesins, invasins, iron uptake systems, are encoded within (PAIs) since they confer pathogenic properties to the respective microorganism. The species of bacteria may have more than one pathogenicity island. For example, in Salmonella, five pathogenicity islands have been identified. The distribution of pathogenic islands in Escherichia coli O157:H7 EDL933 (pathogenic
strain) compared with non-pathogenic laboratory strain MG1655 was illustrated in Fig. 1. Pathogenic strain harbours some islands that were not in the non-pathogenic one. Nearly 30 percent of the 5416 genes encoded by pathogenic *E. coli* lie within these islands. Some are putative virulence factors, meaning that they have been recently identified and warrant further investigation. Others are well-established players in the disease process. [5].

**Fig 1.** Circular genome map of EDL933 (pathogenic strain) compared with non-pathogenic laboratory strain MG1655. Outer circle shows the distribution of islands: shared co-linear backbone (blue); position of EDL933 - specific sequences (O - islands) (red); MG1655 – specific sequences (K - islands) (green); O – islands and K - islands at the same locations in the backbone (tan); hypervariable (purple) [12].

### 4. Mechanisms of bacterial pathogenicity

Many diverse bacterial pathogens share common mechanisms in terms of their abilities to adhere, invade, and cause damage to host cells and tissues, as well as to survive host defences and establish infection. A diagrammatic overview of some of these mechanisms is shown in Fig. 2. The molecular strategies used by bacteria to interact with the host can be unique to specific pathogens or conserved across several different species. A key to fighting bacterial disease is the identification and characterization of all these different strategies.
Fig 2. An overview of bacterial mechanisms for pathogenicity. (A) Upon encountering a human host, a bacterial pathogen may illicit several host responses and use a variety of mechanisms to evade the host defences. (B) Once adhered to a host surface, a bacterial pathogen may further invade host tissues [13].

5. Quorum sensing

Before 1990’s the common view for the microbial world was that the bacteria functioned essentially as individual cells rather than as colonies. However, over the past 20 years this view has been changed. Bacteria were shown to communicate and perceive information from bacteria themselves, animals and plants [14, 15]. One of the important ways of communication is quorum sensing. Quorum sensing is identified as “a phenomenon in which a low molecular weight pheromone accumulates extracellularly, allowing individual cells to sense when the minimal population unit of bacteria has been achieved for a concerted population response to be initiated” [16]. This phenomenon allows bacteria to monitor the surrounding environmental conditions and to coordinate gene expression with population densities. This results in controlled expression of a wide range of behaviour responses (motility, formation of fruiting bodies, sporulation, development and differentiation) and processes (bioluminescence, production of secondary metabolites pigments, HCN, antibiotics, enzymes and virulence factors) [14-18].

Most of the quorum sensing systems in Gram negative bacteria rely on three main constituents; the acyl homoserine lactone signal molecule (AHL), the signal generator (LuxI family) and the signal response transcriptional regulator (LuxR family) (Fig. 3). Quorum sensing was originally discovered in the bioluminescent marine bacteria, *V. fischeri* and *V. harveyi* in the early 1970s [19]. Initially, most of the research on understanding bioluminescence regulation focused on *V. fischeri*. When free living and at low cell density, the culture of *Photobacterium* (now *Vibrio*) *fischeri* appeared dark or dim, but when cells grew and reached a critical density, the population emitted blue green light. The bacterial bioluminescence provides the host fish with light which can act as a mean of communication, attraction or defense and in turn provide the bacteria with a suitable habitat [20]. This bacterium colonizes the light organs of a variety of marine fishes and squids, where it occurs at very high densities (10^10 cells ml^-1) and produces light [21].
Fig 3. Basic model for LuxI/LuxR quorum sensing system. LuxI homologue synthesizes AHL which interacts with LuxR homologue allowing it to bind to and activate transcription of genes encoding various cellular functions [22].

The bioluminescence gene cluster of *V. fischeri* consists of eight *lux* genes (*luxABCDEG*, *luxI* and *luxR*) which are organized as two divergent transcriptional units [23, 24]. The products of the *luxI* and *luxR* genes function as regulators of bioluminescence [25]. The *luxA* and *luxB* genes encode the α and β subunits of luciferase enzyme respectively. *luxC, luxD* and *luxE* genes encode products that form a multi-enzyme complex that converts the long chain fatty acid into the aldehyde substrate utilized by the light-producing enzyme luciferase [26, 27]. The energy produced from this reaction is seen as blue-green light [28]. *luxG* codes for a protein of unknown function [29]. Luciferase can constitute 5% or more of the cellular protein [30] and 10% or more of the cellular energy can be utilized in producing light [31]. In 1970, Nealson et al. reported that *V. fischeri* produced an extracellular factor, an autoinducer, which regulated production of the light-producing enzyme luciferase. The autoinducer was later shown to be 3-oxo-N(tetrahydro-2-oxo-3-furanyl) hexanamide, more commonly known as N-3-(oxohexanoyl) homoserine lactone [32].

6. Conclusion

Quorum sensing is a process of cell-cell communication that allows bacteria to share information about cell density and adjust gene expression accordingly. This process enables bacteria to express energetically expensive processes as a collective only when the impact of those processes on the environment or on a host will be maximized. Here we tried to write a short review about the quorum-sensing and bacterial pathogenicity. QS is a vital regulatory mechanism used by many bacteria to control collective traits that allow bacteria to exploit particular niches. The virulence factors were determined both quantitatively and qualitatively. It was found that the incidence of virulence factors was different, independent and strain specific among all genera. Depending on researches by many scientists that virulence factors were controlled by QS phenomenon, it was suggested to use a different synthetic furanone derivatives as well as natural plants to suppress the quorum sensing activity, hence inhibit or attenuate the virulence factors of the tested pathogenic clinical isolates. Our studies introduces not only a new mode of action and possible validation for traditional plant use, but also a potentially new therapeutic direction for the treatment of bacterial infections via inhibiting the bacterial virulence factors.

Acknowledgements: The support by department of Microbiology, Faculty of Sciences, Ain Shams University, Cairo, Egypt is gratefully acknowledged.

References


